

does not fall into the "ectomy" class. Appendicectomy and tonsillectomy leave no room for recurrent inflammation in the organs involved. No doubt removal of the antrum would be followed by a complete cure of antritis. But the cure would be much worse than the disease. It is possible to cure inflammation in a sinus completely by adequate treatment, but of course the sinus remains, and so does the inherent liability to infection of it which caused the original trouble.

Of the 100 children we have been discussing fifty-two were completely cured—that is, they were free of symptoms, and final radiographs showed normal sinuses; thirty-two were improved; and sixteen remained unchanged.

Relation of Tonsils and Adenoids to Sinusitis

Even in a short paper one cannot omit referring to the tonsils and adenoids and their relation to sinusitis. The first question that comes to mind is, "Does infection of the tonsils and adenoids cause sinusitis?" If so it must be either because the adenoids are so large as to block the nasal airway and interfere with ventilation of the sinuses, or because it is a result of surface spread of infection against the normal mucous stream kept up by the cilia. The removal of tonsils and adenoids should cure sinusitis, and it should be uncommon among children who have had their tonsils and adenoids removed. I have already mentioned that of twenty-four cases of sinusitis in children only nine cleared up after removal of the tonsils and adenoids, and they might have done so without the operation. Of the 100 children with sinusitis forty-one had already had their tonsils and adenoids removed completely. The broad conclusion is justifiable that disease of the tonsils and adenoids is not a common cause of sinusitis and that their removal is neither a preventive nor a cure of the condition.

The second question is, "Does inflammation in the sinuses give rise to infection of the tonsils and adenoids?" As the post-nasal stream of mucus is over the adenoids and posterior halves of the tonsils the mechanical possibility of such an infection is evident. It is difficult to draw conclusions from the fact that forty-one of our 100 children had previously had their tonsils and adenoids removed. They may have had the operation done for symptoms which should more properly have drawn attention to the sinuses. Even worse, they may have developed sinusitis as a result of imperfect technique during the operation of removal of their tonsils and adenoids. One has seen that happen. Infected blood runs into the sinuses and sets up inflammation there.

I believe that sinusitis is a common cause of inflammation of the adenoids, and to a lesser degree of the tonsils. The first step in the treatment of sinusitis is the treatment of the sinus itself, and not the removal of the tonsils and adenoids. If the latter are infected and fail to respond to such treatment they should be removed. If there is a large pad of adenoids interfering with respiration, treatment of coexisting sinusitis is not likely to lead to cure until it is removed.

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A CLINICAL EXPERIMENT IN OESTRIN THERAPY

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Oestrin is now well established as a therapeutic agent, but many problems remain to be solved before the most effective mode of administration can be determined. The principle of endocrine therapy is to give the hormone by the most convenient route in such a form and dosage that it will be delivered at the site of effect at a suitable rate, in suitable concentrations, and over as prolonged a period as possible or desirable. The following case illustrates some of the factors to be considered in the use of oestrin.

On February 27, 1936, Mr. Frank Cook did a bilateral ovariectomy, for cysts of both ovaries, on a girl, aged 20, who had suffered for some time from irregular menstrual bleeding. Three days later uterine haemorrhage started and continued for three days. Nine days after the operation hot flushes began to appear. Oestrin was first given forty-four days after operation, by which time the patient was complaining of about twelve hot flushes a day, and during the subsequent two years the case afforded an opportunity for studying the effects of oestrin given by mouth, by injection, and by implantation. In Chart I the number of daily hot flushes is indicated, and is correlated with the dose of oestrin administered.

The Effective Dose of Oestrin for a Recent Castrate

A consideration of the chart shows that the symptoms as measured by the daily frequency of hot flushes began to come under control when oestrone (menformon, Organon) was given in daily doses of 6,000 I.U. (0.6 mg.) by mouth, and after a prolonged period of administration of higher doses remained completely controlled by 5,000 I.U. daily. The case is particularly suitable for this type of investigation, since the daily hot-flushes curve rose rapidly when treatment was discontinued. Later in the patient's history (January, 1937, et seq.) doses increasing from 1,000 I.U. of oestrone by injection had an effect on the symptoms; and later still (October, 1937) 5,000 M.U. of oestriol by mouth* (tridestrin, Paines and Byrne) was found to be a suitable maintenance dose. Finally the implantation of a 14 mg. tablet of crystalline oestrone produced a demonstrable effect lasting over a period of weeks.

Thus it would appear that relatively small doses of oestrin by mouth are effective in controlling the symptoms of acute ovarian deficiency in a castrate. This observation is supported by results obtained in other cases. For instance, the administration of 1,000 I.U. daily for a fortnight, followed by 2,000 I.U. for another fortnight, completely relieved the symptoms of a woman of 54 who was suffering from a moderately severe menopause with six hot flushes a day, and converted a well-marked menopausal vaginal smear into one typical of oestrus.

It is important to determine the minimal effective maintenance dose of oestrin in these cases, for the administration of high doses has certain disadvantages:

1. It may induce uterine haemorrhage, and the patient suffering from the effects of a natural menopause should be

* Oestriol (tri-hydroxy-oestrin) is less potent when given by injection than oestrone (keto-hydroxy-oestrin), but it is more effectively absorbed than oestrone when given by mouth. It therefore appears to be a suitable method of peroral administration of oestrin.

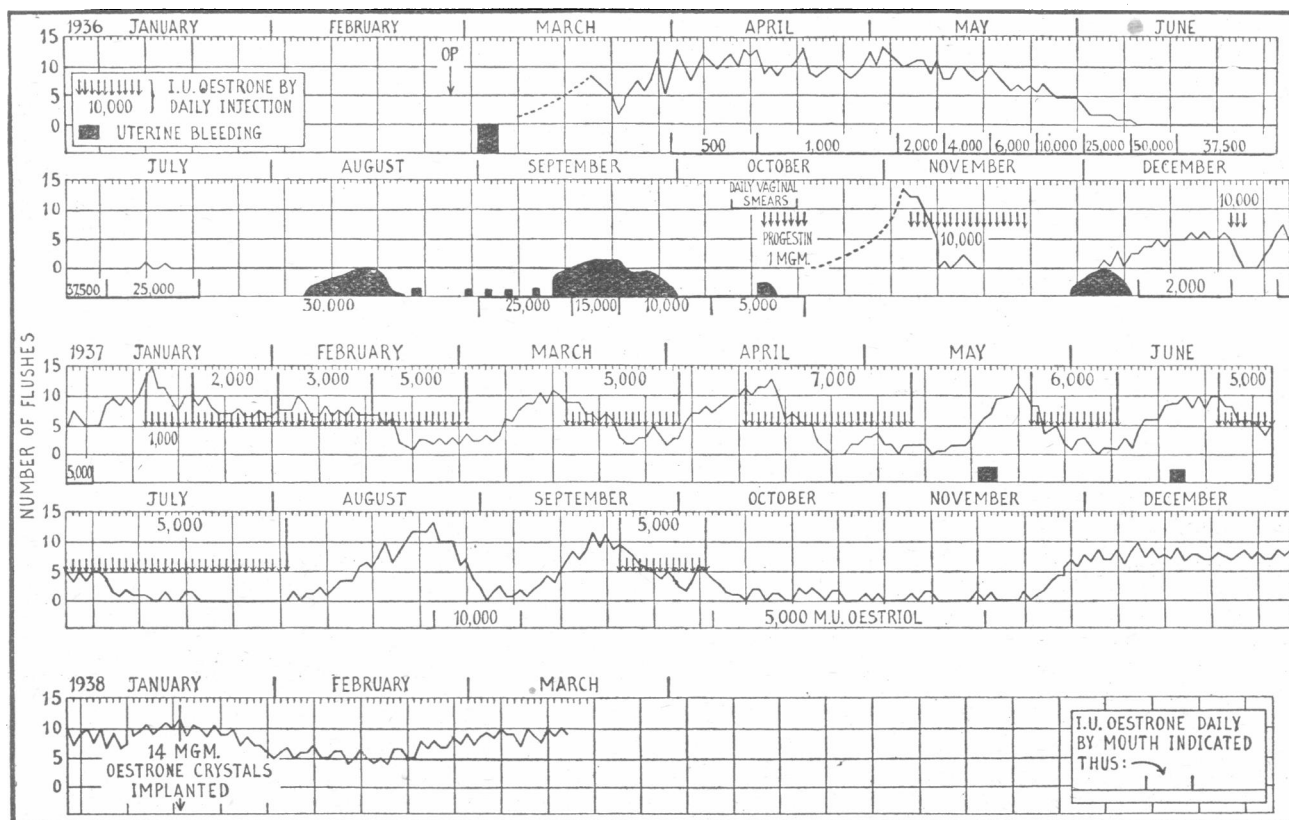


CHART I.—Showing the number of hot flushes daily and their correlation with the dose of oestrin administered.

warned of this possibility if moderately high-dosage oestrin therapy is contemplated.

2. It may give rise to certain uncomfortable symptoms such as a feeling of fullness, headaches, and nausea, which are probably moliminal in nature and are due to dosage slightly below that which would produce oestrin-withdrawal bleeding.

3. It may inhibit the gonadotropic activity of the anterior pituitary gland. The sudden or gradual diminution of ovarian function in the castrate or at the menopause produces excessive gonadotropic activity, and it is the disturbance of balance between these two endocrine secretions that is responsible for the symptoms of the menopause. The action of oestrin in minimal effective doses is to accustom the organism to the new level of hormone activity, whereas the administration of unnecessarily high doses inhibits pituitary function and merely postpones the appearance of menopausal symptoms until oestrin therapy is discontinued.

Oestrin Threshold Bleeding

From the beginning of August to the middle of October, 1936, intermittent uterine haemorrhage was taking place. Observations by Zuckerman (1937) on the cause of uterine haemorrhage in primates have revealed the fact that there are three significant levels of oestrin utilization by the uterus. (The term "oestrin utilization" is preferred to "oestrin concentration," since two factors are concerned—the concentration of oestrin in the blood reaching the endometrium, and the degree of sensitivity of the endometrium to oestrin.) These levels are (1) subthreshold, (2) threshold, and (3) superthreshold (see Chart II). The superthreshold level is indicated by uterine haemorrhage occurring a week or so after the dose of oestrin is lowered or completely withdrawn. This is known as "oestrin-withdrawal bleeding." The threshold level is shown by intermittent bleeding occurring during the period of administration of oestrin—"oestrin threshold bleeding."

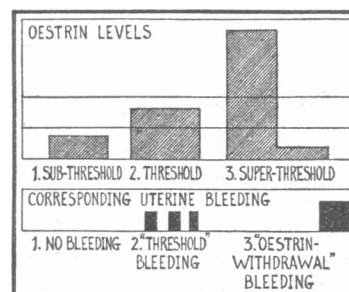


CHART II.—The effect of different levels of oestrin.

Zuckerman points out that this type of haemorrhage tends to occur in forty-two-day cycles. The subthreshold level fails to produce bleeding either during or after the period of administration. The haemorrhage which occurred in August could not have been oestrin-withdrawal bleeding, since the daily peroral dose of oestrone had been raised from 25,000 to 30,000 I.U. (2.5 to 3 mg.) a fortnight previously. Nor can the haemorrhage in September be regarded as a withdrawal bleeding, for the dose had been lowered only from 30,000 to 25,000 I.U. It seems probable, therefore, that this represents threshold bleeding, and it may be noted that the two main bouts of haemorrhage occurred at an interval of thirty-seven days, which approximates fairly closely to Zuckerman's forty-two-day interval. It will be seen that the dose of oestrin required to produce threshold bleeding is about five times higher than that required to relieve subjective symptoms such as hot flushes.

The calibration of the threshold-bleeding level is important, since it provides information as to the physiological dose of oestrin requisite for proliferative development of the endometrium, and consequently suggests the dosage

necessary to stimulate the endometrium in cases of amenorrhoea. An attempt was therefore made to determine the level for threshold bleeding when oestrone was given by injection. Administration of 10,000 I.U. (1 mg.) of oestrone by injection daily for a fortnight induced withdrawal bleeding after a seven-day interval. Later (April, 1937) a three-weeks course of 7,000 I.U. by injection and a fortnight's course of 6,000 I.U. gave rise to withdrawal bleedings nine and eight days after administration was discontinued, whereas a seven-weeks course of 5,000 units by injection did not produce uterine haemorrhage. Thus it would appear that the intramuscular dose of oestrin necessary to produce threshold bleeding in this case is between 6,000 and 5,000 I.U. (0.6 and 0.5 mg.), whereas the oral dose was found to be between 25,000 and 30,000 units, suggesting that oestrone is about five times as effective by injection as by mouth. This agrees with the observations on the relief of subjective symptoms (frequency-of-hot-flushes curve)—namely, that 5,000 units by mouth and 1,000 units by injection diminished the number of hot flushes.

It is not suggested that 5,000 I.U. represents the bleeding threshold of all castrated women. It is obvious that this level depends on factors such as the degree of atrophy of the endometrium at the time the experiment is begun and the individual sensitivity of the subject's reproductive tract to oestrin. For instance, in the case of another castrate, a three-weeks course of daily injections of 1,000 I.U. for fourteen days, followed by 2,000 I.U. for seven days, provoked an oestrin-withdrawal bleeding five days later, whereas a fortnight's course of 1,000 I.U. daily provoked no withdrawal haemorrhage. Her bleeding threshold would therefore appear to be between 1,000 and 2,000 I.U. daily.

Effect of Implantation of a Tablet of Crystalline Oestrone

Parkes (1938) has recently drawn attention to the fact that the duration of effect of an endocrine preparation is inversely proportional to its solubility in the body fluids. For this reason the administration of oestrone or oestradiol by injection in the form of the monobenzoate prolongs the effect by diminishing the rate of absorption from the site of injection. The pure crystalline hormone, administered in solid form and not in an oily solution, appears to be absorbed considerably more slowly, and Deanesly and Parkes (1937) have shown that the implantation and reimplantation of a single 6 mg. tablet of compressed crystalline testosterone into a series of castrated rats for ten-day periods demonstrated its effectiveness over a total of 130 days.

This method has been employed in the case under discussion. The hot-flushes-frequency curve was allowed to reach a plateau at a fairly high level (about ten to twelve a day), and then on January 17, 1938, a 14 mg. (140,000 I.U.) tablet of compressed pure crystalline oestrone was placed beneath the skin of the abdominal wall. The hot-flushes-frequency curve began to descend in about a week and reached a trough at four to six daily about four weeks after implantation, after which it gradually rose again, reaching a level of eight to ten daily flushes about seven weeks after implantation. Assuming that absorption from the surface of the crystal occurred at a constant rate (though there is no evidence to support this assumption), and taking the period of effectiveness as four to five weeks (twenty-eight to thirty-five days), it may be calculated that the daily absorption corresponded to 0.4 to 0.5 mg. (4,000 to 5,000 I.U.). An examination of Chart I

shows that the effect of the implantation on the hot-flushes-frequency curve is very similar to that of daily injections of 5,000 I.U. (see February, 1937).

The inference is that the dosage used in this case was too low and that the effect might have been more marked and prolonged if a crystal of greater weight had been implanted. Taking these facts into consideration, it would appear that this new method of hormone administration represents a significant advance in the field of endocrine therapy.

Summary

Experiments performed on a human female castrate are described:

1. Administration of oestrin in quite small doses by mouth was effective in controlling symptoms.
2. The level of oestrone threshold bleeding was found to be between 6,000 and 5,000 I.U. by injection and 25,000 and 30,000 I.U. by mouth, suggesting a peroral/intramuscular ratio of 5:1.
3. A 14 mg. tablet of crystalline oestrone was implanted subcutaneously, and was effective in controlling symptoms for four or five weeks.

I should like to acknowledge my indebtedness to my colleagues in the endocrine clinic, Dr. A. C. Hampson and Mr. H. A. Hamilton, for their interest and co-operation in this experiment; and to thank Dr. A. S. Parkes for supplying me with the tablet of crystalline oestrone, Dr. A. N. Macbeth of the Organon Laboratories for generous supplies of menformon, and Messrs. Paines and Byrne for supplies of oestriol (tridestrin).

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G. Crile (*Clev. clin. Quart.*, January, 1938, p. 33) discusses the diagnosis and treatment of essential hypertension. There is an increase in the diastolic blood pressure, changes in the optic disks and in the kidneys, and a history of disability and distress. Sclerosis may become established if hypertension begins in early life. It is urged that when hypertension has reached the malignant phase the risk of operation in the hope of curing or relieving the symptoms is justified. In a series of sixty-nine consecutive cases symptomatic improvement was noted in 95 per cent. on discharge from hospital. Surgical treatment of essential hypertension was carried out on the adrenal sympathetic system in 213 patients, a total of 358 operations being performed. Of these, 206 were coeliac ganglionectomies in 129 patients. It was found that this operation with denervation of the adrenal glands gave the most encouraging results. It does not interfere with metabolism, or with the function of the digestive or genito-urinary tract. It was found that many patients were completely relieved of symptoms after operation, while a large majority experienced considerable relief. Among the last 112 individual coeliac ganglionectomies there have been only two deaths. It was considered that impaired kidney function was a contraindication to the operation, but the early results in two cases in which glomerulonephritis was associated with essential hypertension have led the author to believe that this may not be correct. A final judgment regarding the end-results of coeliac ganglionectomy cannot yet be made, but it is suggested that the symptomatic relief, the improvement in the blood pressure, and the fact that many patients are able to return to their usual occupation make this form of operative treatment well worth while.